Bacteria That Masquerade as Fungi
Actinomycosis/Nocardia

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The order Actinomycetales includes phylogenetically diverse but morphologically similar aerobic and anaerobic bacteria that exhibit filamentous branching structures which fragment into bacillary or coccoid forms. The aerobic actinomyces are a large, diverse group of gram-positive bacteria including *Nocardia, Gordona, Tsukamurella, Streptomyces, Rhodococcus, Streptomycetes, Mycobacteria,* and *Corynebacteria.* The anaerobic genera of medical importance include *Actinomyces, Arachnia, Rothia,* and *Bifidobacterium.* Both *Actinomyces* and *Nocardia* cause similar clinical syndromes involving the lung, bone and joint, soft tissue, and the central nervous system. The medically important *Actinomyces* organisms cause infections characterized by chronic progression, abscess formation with fistulous tracts and draining sinuses. Called "great masqueraders," diagnosis of actinomycosis and nocardiosis is often delayed. Once recognized, treatment of these infections requires long courses of parenteral and oral therapy. This review will compare and contrast infections due to *Actinomyces* and *Nocardia.*

Keywords: *Actinomyces*; *Nocardia*; filamentous bacteria

Actinomycetes are a group of aerobic and anaerobic bacteria in the order Actinomycetales. These organisms are phylogenetically diverse but morphologically similar, exhibiting characteristic filamentous branching structures which then fragment into bacillary or coccoid forms (1) (Figure 1). The name actinomycosis means "ray fungus," and the organisms may resemble fungi owing to their filamentous appearance. Aerobic actinomyces are a large, diverse group of gram-positive bacteria (2). Species associated with human and veterinary disease include *Nocardia*, *Gordona*, *Tsukamurella*, *Streptomyces*, *Rhodococcus*, *Streptomycetes*, and *Corynebacteria*. Anaerobic genera of medical importance include *Actinomyces*, *Arachnia*, *Rothia*, and *Bifidobacterium*. Both *Actinomyces* and *Nocardia* cause similar clinical syndromes involving the lung, bone and joint, soft tissue, and the central nervous system. Called "great masqueraders," diagnosis of actinomycosis and nocardiosis is often delayed. The hallmark of both infections is abscess formation and chronic progression of infection without regard to anatomic barriers. Patients frequently present with fistulous tracts and draining sinuses. Likewise, treatment of these infections require long courses of parenteral and oral therapy (e.g., months to years). This review will compare and contrast infections due to *Actinomyces* and *Nocardia*.

MICROBIOLOGY

Actinomycosis

The genus *Actinomyces* comprises a group of 42 species and 2 subspecies (3). Classification of these organisms has traditionally relied on phenotypic testing: *Actinomyces* are indole negative, and species may be differentiated by colony morphology and biochemical characteristics. However, such phenotypic tests have resulted in misidentification (4), and classification based on genotypic methods, including 16S ribosomal RNA (rRNA) and DNA probe analysis, has been useful in definitive identification (4–7). These methods have led to identification of new *Actinomyces* species and reclassification of some actinomycetes as *Arcanobacterium* or *Actinobaculum* species.

The most common cause of human disease among the *Actinomyces* species is *A. israelii*. Other less frequent agents of human infection include *A. naeslundii*, *A. odontolyticus*, *A. viscosus*, *A. meyeri*, and *A. gerencseriae*. New species identified by molecular techniques have led to an increasing number of agents of actinomycosis, including *A. europaeus*, *A. neuii*, *A. radingae*, *A. graveenitzii*, *A. turicensis*, *A. cardiffensis*, *A. houstonesis*, *A. hongkongensis*, and *A. funkei* (3, 7).

Nocardiosis

The genus *Nocardia* are gram-positive organisms that are partially acid fast due to the mycolic acid content of the cell wall (2). *Nocardia* species are now classified using a range of genotypic and phenotypic data, and combinations of such characteristics have been used to describe many novel species (8–12), more than 30 having been described in the last decade. At least 89 species of *Nocardia* are officially recognized to date (3), of which as many as 30 are considered to be of medical importance (2, 3). Nocardiae are common in the environment worldwide, including various soil, freshwater, marine-water, and organic-matter habitats, where they are believed to maintain a saprophytic existence (2, 13, 14). *Nocardia* species may also be present in domestic environments such as house dust, garden soil, beach sand, and swimming pools (14). Rarely, they may be found as transient colonizers of the skin and upper respiratory tract (14). However, isolation of *Nocardia* from patients should be carefully evaluated for the presence of disseminated disease, especially in immunocompromised hosts.

Nocardia species were originally classified on the basis of biochemical properties. However, classification has become more complex with the use of antibiotic susceptibility profiles, which have revealed marked heterogeneity (15), and molecular techniques, such as analysis of the 16S rRNA gene and restriction fragment length polymorphisms (16–19). *N. asteroides*, formerly considered the most common species associated with human disease, has been redefined as a complex that includes *N. asteroides sensu stricto*, *N. farcinica*, *N. nova*, and *N. cyriacigeorgica* (1, 20–22). Recently, strains of *N. cyriacigeorgica* have been identified as an emerging pathogens responsible for human infection in Western Europe, Greece, Turkey, Japan, Thailand, Canada, and the United States (23–34). Most cases of infection have occurred in the context of human immunodeficiency virus–related or iatrogenic immune suppression.

N. farcinica appears to be more virulent than the other members of the *N. asteroides* complex, since infection with this species is more likely to result in disseminated disease. Further, *N. farcinica* tends to be more resistant to antimicrobials,

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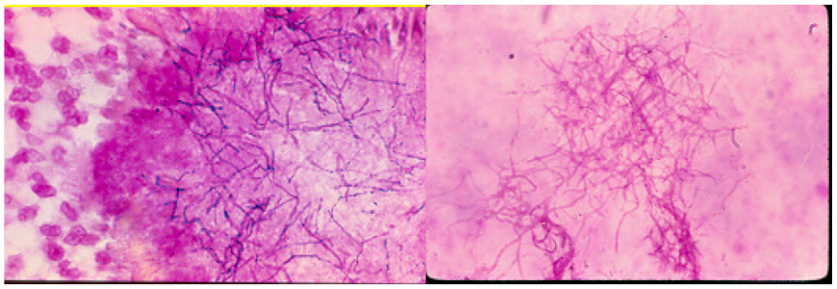

Figure 1. Filamentous Actinomycetes. Anaerobic gram-positive *Actinomyces* species have a beaded appearance in this clinical specimen (*left panel*), while the aerobic *Nocardia* species (*right panel*) stain acid fast in this sputum specimen.

especially third-generation cephalosporins and tobramycin (20, 35). *N. nova* has a different susceptibility pattern, showing consistent susceptibility to erythromycin and ampicillin (21).

Molecular studies indicate that *N. brasiliensis*, *N. otitidiscaviarum*, and *N. transvalensis*, once thought to be fairly homogeneous genera, also exhibit diverse characteristics, and it is anticipated that new species will continue to emerge (36–38).

EPIDEMIOLOGY AND ECOLOGY

Actinomyces are part of the normal flora of the mouth and gastrointestinal tract and are generally low virulence. In contrast, *Nocardia* are saprophytic organisms with a worldwide distribution in soil. Human infections result from direct inoculation of the skin or soft tissue or by inhalation of contaminated soil. Isolation of any species of *Nocardia* from human specimens is significant.

Actinomycosis

Actinomyces species are members of the endogenous flora of mucous membranes and are frequently cultured from the gastrointestinal tract, bronchi, and female genital tract (7). By 2 years of age, nearly 100% of children are colonized by *Actinomyces* (39). The organisms have never been cultured from nature, and no person-to-person spread has been documented (7).

Actinomycosis has been documented in all age groups, with the highest incidence in mid-life and lower frequencies at each end of the age spectrum (7). Infections due to *Actinomyces* are usually associated with the breakdown of normal physical barriers, such as disruption of mucosal membranes in the mouth and gastrointestinal tract (40). Certain conditions may predispose to infection, including erupting secondary teeth, dental extractions and caries, gingivitis, and gingival trauma (41). Actinomycosis is not typically considered an opportunistic infection of immunocompromised hosts. However, diagnosis of actinomycosis in children should alert the astute physician to consider an underlying immunodeficiency such as chronic granulomatous disease (42). Virtually all infections are polymicrobial. The infections are not common, occurring in 1:100,000 in the Netherlands and Germany in the 1960s and 1:300,000 in the Cleveland area during the 1970s (43). Most series report males more frequently infected than females (43–49). Incidence of actinomycosis has decreased with the advent of the antibiotic era and improved dental hygiene. Populations with limited access to dental and/or medical care may be at higher risk than the general population (7). Indeed, adult men with poor oral hygiene seem to be at greatest risk, perhaps contributing to the greater ratio of infection in men.

Nocardiosis

Nocardiosis is also an uncommon gram-positive bacterial infection. *Nocardia* spp. have the ability to cause localized or systemic suppurative disease in humans and animals (12–14, 50, 51). Nocardiosis may be regarded as an opportunistic infection, with clusters of invasive disease documented in oncology and transplant units (1, 52–54). The majority of patients with nocardial infection are immunocompromised, most often with cell-mediated abnormalities (51, 50). In a review of 1,050 cases, for example, 64% were immunocompromised (13). The most common causes were glucocorticoid therapy, malignancy, organ and hematopoietic stem cell transplantation, and HIV infection.

CLINICAL MANIFESTATIONS

Actinomycosis

The major sites of actinomycoses are cervicofacial, abdominopelvic, and thoracic (7, 55–57). Actinomycosis most often presents as a chronic cervicofacial infection with the development of abscesses, draining sinus tracts, fistulae, and tissue fibrosis (7, 44, 45, 58). Disease occurs primarily via direct invasion after dental infections, manipulations, and oromaxillofacial trauma, which cause a break in mucosal integrity and is rarely spread by metastatic or hematogenous routes (59). Cervicofacial actinomycosis generally spreads without regard for anatomic barriers such as fascial planes or networks of lymphatic drainage.

Thoracic disease, which may be mistaken for neoplasm or acute or chronic pneumonia, accounts for 15 to 20% of total cases of actinomycosis (60, 61). It is usually secondary to aspiration of normal flora from the oral cavity, although spread from contiguous cervicofacial actinomycosis, esophageal perforation, or in rare instances hematogenous spread may occur (60). Typically, infection is established in the lung, resulting in an initial acute pneumonitis (61). Infection produces a chronic inflammation, fibrosis, and cavitation that result in the invasion and destruction of surrounding structures (35, 45, 47, 62, 63). Unchecked, it invades the interlobar fissures, pleura, chest wall, soft tissues, and even the mediastinum or bones (64, 65) (Figure 2). It may simulate pulmonary tuberculosis with cough, hemoptysis, night sweats, and loss of weight (61).

Abdominal and pelvic infections are associated with abdominal surgery, tuboovarian abscess, ruptured appendicitis, and intrauterine contraceptive devices (IUCD) (66, 67). Diagnosis of abdominal and pelvic actinomycosis is frequently delayed; months to years may separate the initial break in the physical barrier (i.e., appendicitis, peptic ulcer disease, perforation of the bowel or bowel surgery) and the recognition of clinical disease (7). In abdominal actinomycosis the appendix is the organ most commonly involved, followed by the colon, stomach, and liver. Abdominal actinomycosis most frequently presents an undifferentiated mass, forming abscesses and sinuses (68). Since the hallmark of infection is spread directly through all layers of tissue without regard for physical planes or barriers, the formation of sinuses and fistulas is often seen in skin and bone. Acute inflammatory lesions are surrounded by fibrosing granu-

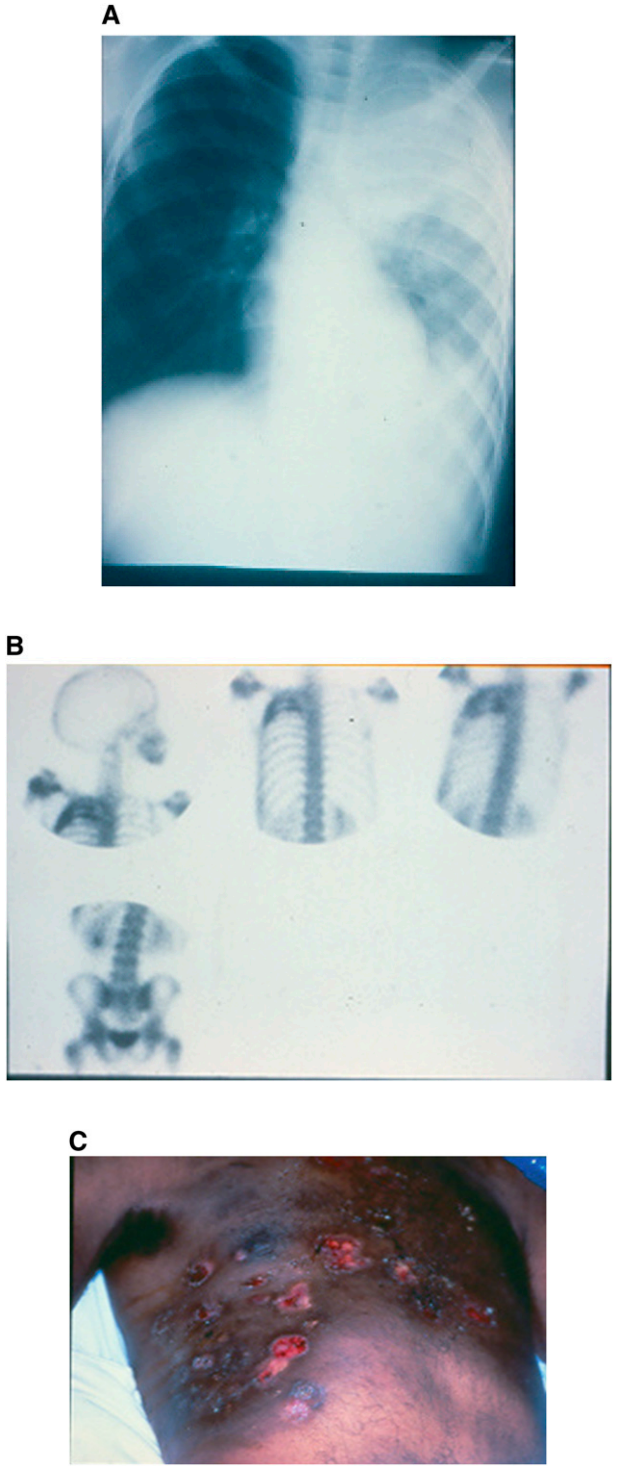

Figure 2. Pulmonary Actinomycosis. *A* shows chronic cavitary disese with volume loss of the left lung. *B* demonstrates dissemination to bone and joints, while *C* illustrates fistulous tracts.

lomatous tissue containing "sulfur granules." In 90% of all cases, a medico-surgical treatment results in complete healing (56).

The incidence of pelvic actinomycosis is higher in patients with an IUCD. The longer a patient has an IUCD, the greater the risk for actinomycetes of the genital track (69). The clinical picture is characterized by chronic intermittent or subacute pain, tenesmus, flatulence, and low-grade fever (66, 67, 69). In most cases, ovarian tumors are suspected and pelvic actinomycosis is diagnosed after surgery (70, 71). The clinical picture is characterized by chronic, intermittent abdominal pain, fever, weight loss, tenesmus, and flatulence. For pelvic actinomycosis, signs and symptoms include abnormal vaginal bleeding or discharge, pelvic pain, fever, and weight loss (7).

Less common sites of actinomycotic infection include central nervous system, musculoskeletal and soft tissue, and, very rarely, disseminated disease. CNS disease typically appears as single or multiple lesions that are ring-enhancing on CT (7). Osteomyelitis caused by actinomycetes primarily involves the mandible, although rare case reports include infections of the hand and humerus (72). Hematogenous spread is rare, with limited dissemination of disease (7).

Nocardiosis

Pulmonary infection by *Nocardia* is an uncommon but serious infection, particularly among the immunosuppressed host. Like the actinomycosis, the disease may be confused with other chronic suppurative lung diseases and malignancy. Pulmonary disease is the most common clinical presentation of *Nocardia* infection, accounting for more than 40% of reported cases (61). Of these, approximately 90% are caused by members of the *N. asteroides* complex (73–77). The majority of isolates in one series, however, were the highly virulent *N. farcinica* (60%) (33).

Nocardia infection causes an acute, frequently necrotizing pneumonia and an associated cavitation (61). Other clinical presentations include an indolent, slowly enlarging pulmonary nodule or pneumonia with an associated empyema. As with mycobacterial and actinomycoses, the clinical picture is slowly progressive and includes fever, chills, productive cough, sweats, weight loss, anorexia, dyspnea, and hemoptysis (54). Radiologic imaging may reveal nodules, reticulonodular or diffuse pneumonic infiltrates, single or multiple abscess, and areas of consolidation, with or without cavitation. *Nocardia* frequently disseminate hematogenously, resulting in metastatic spread, most commonly to the central nervous system (about 33% of all cases) (33). As such, all patients with nocardiosis should have neuroimaging (MRI or CT) to rule metastatic disease.

Nocardiosis usually occurs in patients who have either impaired local pulmonary defenses or systemic immunosuppression due to leukemias, lymphomas, organ transplants, AIDS, and prolonged corticosteroid or cytotoxic therapy (13, 28, 61, 73, 77, 78–80). More recent reviews have noted nocardiosis in immunocompetent hosts with no predisposing factors identified (81–83).

Although 20% of extrapulmonary nocardiosis infections occur in the absence of pulmonary disease, approximately 50% of all pulmonary cases will disseminate to sites outside the lungs, most commonly the brain. Typically, patients present with acute signs of sepsis and intracranial mass effects (1, 84, 85). It should be noted that cerebral abscess in a severely immunocompromised patient may be asymptomatic with a latency period of up to 3 years before typical clinical presentation develops (1).

Direct inoculation of *Nocardia* species by transcutaneous routes results in three forms of infection: cellulitis, lymphocutaneous disease, or actinomycetoma. Unlike pulmonary or disseminated disease, primary cutaneous nocardiosis is usually an infection in immunocompetent hosts (12, 86). Although any species of *Nocardia* may be involved, *N. brasiliensis* is the species most frequently isolated (approximately 80%) from cases of primary cutaneous or subcutaneous nocardiosis.

Primary cutaneous nocardiosis usually occurs in an immunocompetent individual 1 to 3 weeks after some type of local trauma with subsequent environmental contamination of the

wound (12, 54). Cellulitis presents with pain, swelling, erythema, and warmness at the affected sites, which typically do not drain and rarely disseminate to bone, muscles, and joints (12, 54).

Lymphocutaneous nocardiosis is sometimes referred to as "sporotrichoid-type" disease owing to its similar appearance to cutaneous sporotrichosis (86). This *Nocardia* infection is marked by the presence of a primary pyodermatous lesion frequently associated with areas of chronic drainage and crusting. In contrast to primary cutaneous disease, the organism invades more deeply to involve the lymphatic system and progresses to the formation of lymphatic abscesses (12, 54, 86).

Actinomycetoma due to *Nocardia* is a late-stage infection, characterized by a chronic, localized, slowly progressive, and subcutaneous and bone disease, usually involving the foot and often painless (12, 54). Most lesions develop over a period of months to years before diagnosis. Lesions frequently exhibit tumefaction, subcutaneous nodules, destructive granulomata, and formation of intermittent fistulas, with production of pus and granules (1, 86, 87). Actinomycetoma is rare in developed countries.

DIAGNOSIS

The most challenging aspect of diagnosis of infection by members of the Actinomycetes is the inclusion of these organisms in the differential diagnosis of patients with chronic cavitary pulmonary disease, especially the immunocompromised patient. Delay in establishing the correct diagnosis is common due to the nonspecific and diverse clinical presentation of actinomycosis and nocardiosis and the inherent difficulty in cultivating the organisms. Both species present as masqueraders in many clinical presentations. A combination of microbiological, pathologic, and molecular studies may be required for definitive diagnosis.

Actinomyces and *Nocardia* species may be difficult to distinguish histologically as well as clinically (58). The presence of beaded, branching, gram-positive bacilli in any clinical specimen should alert the clinician to consider both aerobic *Nocardia* and anaerobic *Actinomyces*. Additional stains can distinguish acid-fast *Nocardia* species from non–acid-fast *Actinomyces* species (40). Histologic identification of sulfur granules (Figure 3) is pathognomonic for actinomycosis, a feature that also distinguishes these organisms from *Nocardia* species.

A definitive diagnosis of actinomycosis or nocardiosis requires the isolation and identification of the organism from a clinical specimen. When suspected, the clinical laboratory must be alerted so that adequate culture techniques may be employed. Specialized media are not required for culture of members of the either group but the use of semi-selective media may increase isolation rates in the presence of more rapidly growing organisms. Although *Actinomyces* are microaerophilic or facultative, specimens should be transported in anaerobic transport media and cultured under strict anaerobic conditions. *Nocardia* species will grow on standard blood culture media, but the use of selective media such as Thayer Martin with antibiotics may be useful (88).

Commercial identification systems may provide species identification as well as susceptibilities for these unique organisms. However, definitive identification may require molecular techniques for both *Actinomyces* and *Nocardia*.

TREATMENT

Treatment for both actinomycosis and nocardiosis require long-term antimicrobial treatment with parenteral and oral antibiotics. Surgical intervention may be required in selective cases.

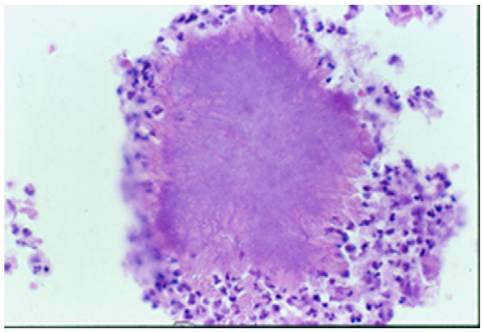

Figure 3. Sulfur granule of *Actimomyces*. These granules are characteristic of actinomycosis.

Actinomycosis

Antimicrobial therapy alone is usually sufficient for the treatment of cervicofacial infection. Thoracic, abdominal, or soft tissue abscesses may require a medico-surgical approach with drainage and extensive resection of affected tissues and excision of sinus tracts combined with prolonged antibiotic therapy (7). Actinomyces are susceptible to penicillins and extended spectrum penicillins, cephalosporins, clindamycin, carbapenems, and tetracycline. Rare isolates of *A. israelii* have developed resistance to penicillin. Treatment is individualized, but most cases require 2 to 4 weeks of high-dose penicillin (e.g., 18–24 million units daily), followed by long-term oral penicillin or amoxicillin for 6 to 12 months. Therapy should be continued until all measurable disease has resolved. For penicillin-allergic patients, doxycycline, erythromycins, and clindamycins have proven to be suitable alternatives. Although monomicrobial therapy with penicillin is usually effective, most infections with actinomycosis are polymicrobial. The role of these organisms in the pathogenesis of actinomycosis is unclear, but some authors recommend adding more broad-spectrum therapy during the early phases of treatment.

Nocardiosis

Management of *Nocardia* infections also requires a combination of appropriate surgical drainage or debridement and chemotherapy (54). Owing to differences in antibiotic susceptibility, isolates of *Nocardia* should be sent to a reference laboratory for precise identification and susceptibility testing. Susceptibility testing is especially important for patients with serious disease, immunocompromised patients, and those patients who fail to respond to initial therapy. Several *Nocardia* species are known to have high frequencies of antimicrobial resistance, such as *N. farcinica* or other newly identified species (54).

Patients with systemic disease require antibiotic therapy. Most authors recommend trimethoprim sulfamethoxazole (5 mg/kg of the trimethoprim component per day) as the drug of choice for mild to moderate disease. For life-threatening pulmonary or disseminated disease, central nervous system disease, and infection in the immunosuppressed patient, combination therapy with TMP-SMX (15 mg/kg intravenously of the trimethoprim component per day in 2 to 4 divided doses) plus amikacin (7.5 mg/kg intravenously every 12 h) is recommended. If CNS disease is present, therapy with ceftriaxone (2 g intravenously every 12 h), cefotaxime (2 g intravenously every 8 h), or imipenem (500 mg intravenously every 6 h) is recommended.

Selected immunocompetent patients who clinically improve on intravenous therapy and have no evidence of CNS disease may be switched to oral treatment to include TMP-SMX

(10 mg/kg of the trimethoprim component per day in 2 or 3 divided doses) and/or minocycline (100 mg twice daily) and/or amoxicillin-clavulanate (875 mg twice daily). Duration of treatment is prolonged, usually 3 to 6 months for cutaneous, 6 to 12 months for serious pulmonary, and a minimum of 1 year for CNS disease.

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